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Identification of Autism Spectrum Disorders associated Long Non-Coding RNAs shows connections to the synaptic transmission pathway.

Brian Gudenas
Clemson University

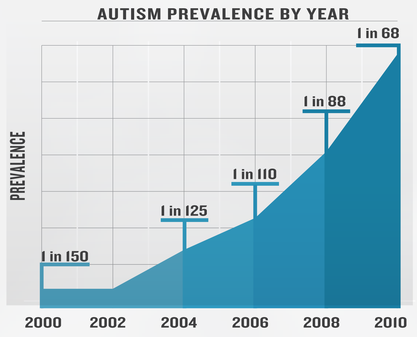
Liangjiang Wang
Clemson University

IDENTIFICATION OF LONG NON-CODING RNAs ASSOCIATED WITH AUTISTIC DISORDER

Brian Gudenas, Liangjiang Wang
Department of Genetics and Biochemistry, Clemson University

AUTISM SPECTRUM DISORDERS (ASD)

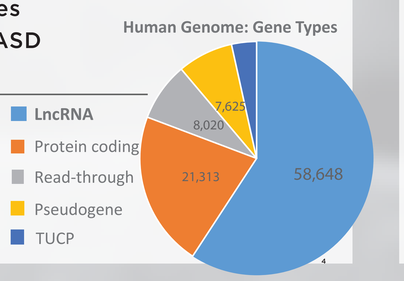
- Neurodevelopmental disorders
- Impaired Social abilities
- Restrictive and/or Repetitive Behaviors
- Estimated $236 Billion total U.S. societal cost in 2013[2]
- 5 times more prevalent in males than females



GENETICS

- 600+ known Autism risk genes (genetically diverse)
- Risk genes predominantly involved in synaptic and chromatin remodeling pathways
- ASD Critical risk periods (mid-fetal, late post-natal)
- Gene expression differences between brain regions in ASD are lessened

Could these novel regulatory LncRNAs be factors causing the gene dysregulation underlying ASD development?



EXPERIMENTAL DESIGN

Identify and examine the relationships between long non-coding RNAs (LncRNAs) differentially expressed in the autistic brain with known autism risk genes. Next, we costruct a weighted gene co-expression network to elucidate the functional roles of these previously uncharacterized non-coding genes and their associations to ASD.

GENE LISTS

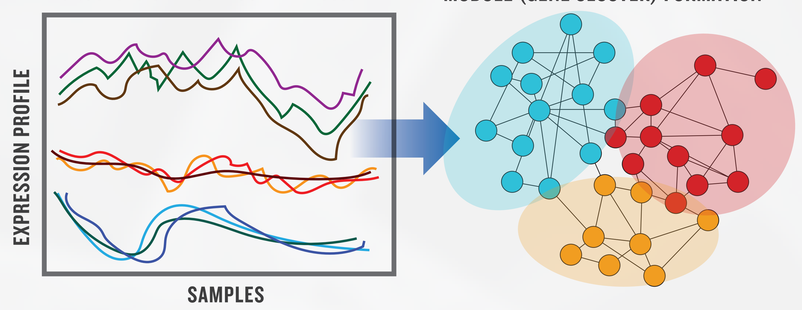
- Differentially expressed genes and LncRNAs (Temporal cortex of the Autistic brain)
- Simons Foundation Autism Research Initiave known autism risk genes
- RBFOX1 (regulates tissue specific alternative splicing) Targets

EXTRACT EXPRESSION PROFILES

- BrainSpan Developmental Transcriptome Dataset[3]
  - 27 brain regions comprised of 524 total samples
  - Age of samples : 8 weeks post-conception to 40 years old

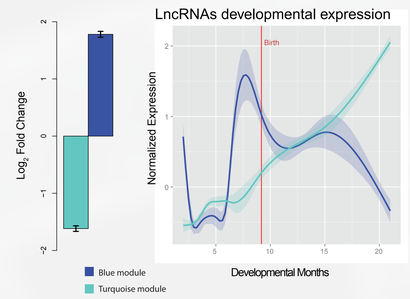
GROUPING GENES BY CO-EXPRESSION

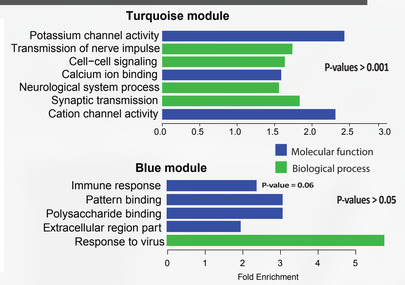
MODULE (GENE CLUSTER) FORMATION



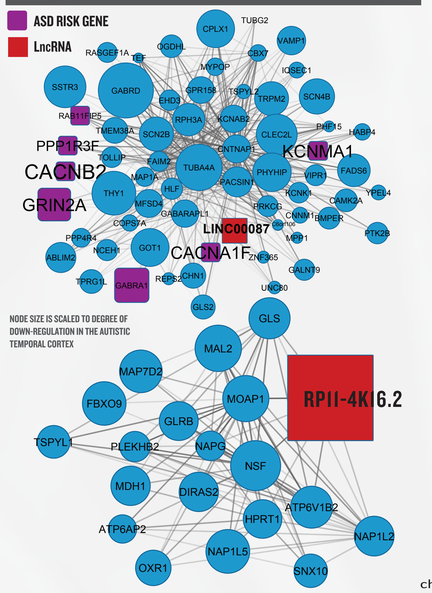
RESULTS

LONG NON-CODING RNA CONTAINING MODULES SHOW ASD CHARACTERISTICS

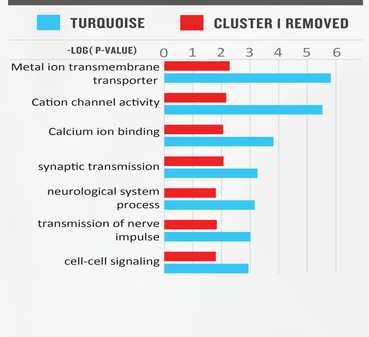




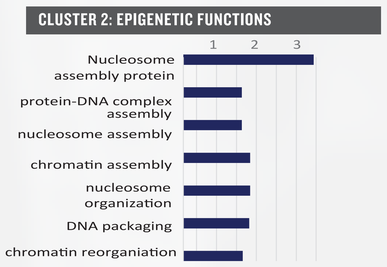
TURQUOISE INTRA-MODULAR HIGH DENSITY CLUSTERING



TURQUOISE MODULE GENE ENRICHMENT



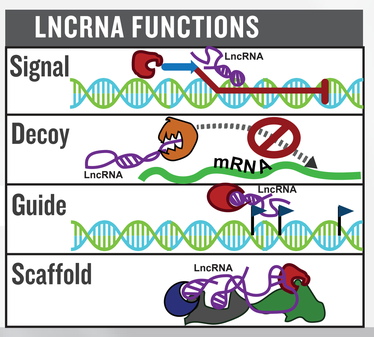
CLUSTER 2: EPIGENETIC FUNCTIONS



LONG NON-CODING RNA

- Long non-coding RNAs (LncRNAs) do not encode proteins
- Once thought of as pieces of "Junk DNA"
- Emerging as major players in gene regulation

LNCRNA FUNCTIONS



Signal for gene repression

Act as a microRNA sponge protecting mRNA from degradation

Recruit chromatin modifiers to specific genomic locations.

Scaffold for a Ribonucleoprotein complex.

CONCLUSION

- Identified 83 differentially expressed lncRNAs in the ASD brain
  - (43 down-regulated, 40 up-regulated)

Gene Co-expression Network Analysis in BrainSpan developmental

- Two high lncRNA containing modules have peak expression values at known critical ASD risk periods (mid-fetal and early post-natal).
- 19 lncRNAs clustered into the synaptic transmission module;
  - Two lncRNAs (LINC00087 and RP11-4K16.2) are present in highly interconnected sub-clusters within the synaptic module.
    1. Cluster 1 represents a driving force for the entire modules cation transporter enrichment, with LINC00087 co-expressed with hub genes
    2. Cluster 2 is enriched for chromatin remodeling activity with lncRNA RP11-4k16.2 showing extreme down-regulation in ASD

FUTURE

Through this study we prioritized autism associated LncRNAs in the brain; now, we will examine them in the more accessible blood samples. Collaborating with the Greenwood Genetics Center we are currently analyzing RNA-seq data from blood samples of autistic patients. Finding aberrant expression levels of our prioritized lncRNAs in the blood samples of autistic patients could open the door to developing a test for a blood sensitive autistic biomarker.

SELF REGIONAL HEALTHCARE

1. Report MW. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network , 11 Sites , United States , 2010. 2014;63(2). 2. Buescher AVS, Cidav Z, Knapp M, Mandell DS. Costs of Autism Spectrum Disorders in the United Kingdom and the United States. JAMA Pediatr. 2014;19104(8):1–8. doi:10.1001/jamapediatrics.2014.210. 3. BrainSpan, 2013. BrainSpan: Atlas of the Developing Human Brain [Internet]. http://www.brainspan.org 4. Iyer MK, Niknafs YS, Malik R, et al. The landscape of long noncoding RNAs in the human transcriptome. 2015